Sequestration of transcriptional regulators by the lenalidomide–cereblon complex for targeting myeloid leukemia

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Abstract**:** Hematopoietic malignancies result from dysregulated self-renewal pathways and an altered differentiation program. Understanding this altered differentiation is essential for identifying novel therapeutic targets in myeloid leukemias. Targeting RNA-binding proteins like the eIF3 complex are growing and attractive targets for selectively altering the translational program expressed in these cells. Here, we will examine the effects and translatability of a conceptually novel approach to recruit and sequester the RNA-binding protein eIF3i to a complex with the E3 ligase substrate adaptor cereblon (CRBN) using the clinically relevant ligand lenalidomide and a new developed analog SL1. We will first examine the structural interface of the ternary complex between eIF3i–lenalidomide–CRBN to drive structure–activity relationship studies for the development of novel and selective eIF3i small molecule recruiters. Second, we will mechanistically evaluate the effects of eIF3i sequestration on the downstream translational program. Third, we will use these insights to understand the effects of eIF3i sequestration on myeloid leukemia cells to evaluate targeting eIF3i with small molecule recruiters as a potentially novel therapeutic strategy. These studies will provide novel insight to the mechanism of action of cancer therapeutics that target CRBN, including lenalidomide, and enable new paradigms in accessing RNA binding proteins and translational factors as druggable targets.